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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,772	06/15/2000	DEREK O'HAGAN	PP01388.202	7681

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EXAMINER	
BRUMBACK, BRENDA G	
ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 04/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/581,772	O'HAGAN ET AL.	
	Examiner	Art Unit	
	Brenda G. Brumback	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-19 and 21-68* is/are pending in the application.

4a) Of the above claim(s) *9,17-19,21-42,48-53 and 60-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10-16,43-47 and 54-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-16, 43, and 44-47, with the species election of a polynucleotide and an adjuvant, in Paper No. 5, is acknowledged. The traversal is on the ground(s) that the earlier filed International application No. PCT/US99/17308 was indicated to have unity of invention. This is not found persuasive for the following reasons.

An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The outstanding claims are drawn to compositions comprising microparticles comprising a poly(α-hydroxy acid) polymer, a cationic or anionic detergent, a polynucleotide adsorbed to the surface of the microparticle, and an adjuvant encapsulated within the microparticle. Levy et al. (WO 96/20698) teach such compositions, as is set forth *infra*. The technical feature of the outstanding claims does not make a contribution over the prior art and is thus not considered to be a special technical feature which fulfills unity of invention. Furthermore, the U.S. PTO is not bound by a finding of unity in the international application in the prosecution of the national stage application.

The requirement is still deemed proper and is therefore made FINAL.

The amendment filed 01/23/2002 is acknowledged. Claims 8 and 20 were canceled. Claims 1-3, 9-14, 17, 21-24, 27, 29, 34, 36, 43, and 44 were amended. Claims 52-68 were added. Newly added claims 52 –59 correspond to elected Group I. Newly added claims 60-67 correspond to Group II. Newly added claim 68 corresponds to Group V.

Claims 1-7, 9-19, and 21-68 are pending. Claims 17-19, 21-42, 48-51, and 60-68 are withdrawn from consideration as directed to nonelected inventions. Claims 9, 52 and 53 are withdrawn from consideration as directed to nonelected species. Claims 1-7, 10-16, 43-47 and 54-59 are under examination on the merits to the extent that they read on the elected species of a polynucleotide and an adjuvant.

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

Claims 2-7, 10-16, 44-47, and 54-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 3, 28, 44 and 45 recite a macromolecule selected from a transcription or translation mediator, an intermediate in a metabolic pathway, an immunomodulator, and a pharmaceutical, among others. The disclosure fails to teach what is encompassed within the definition of these terms; therefore, the metes and bounds of the claimed invention cannot be determined and the claim is indefinite.

Claim 30 recites "gp120". The term "gp120" does not have a clear meaning because it is not accompanied by the name of the virus with which the protein or antigen is associated. This rejection may be overcome by amending the claim to recite something such as "HIV-1 gp120".

Claim 15 is indefinite for recitation of "a member", as it is unclear what the adjuvant is a member of. It is suggested that this phrase be deleted.

Claim 15 is also indefinite for recitation of adjuvant species in a Markush group by the abbreviations only. The claims should be amended to recite the full name of the adjuvant (where appropriate) followed by the abbreviation in parenthesis, *i.e., E. coli* heat-labile toxin-K63 (LT-K63), for example.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 11, 13, 14, 43-47, and 54-57 are rejected under 35 U.S.C. 102(a) as being anticipated by Levy et al. (WO 96/20698).

The claimed invention is drawn to a microparticle comprising a cationic or anionic detergent and a polymer selected from a poly(α -hydoxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, and a polyanhydride and further comprising a polynucleotide adsorbed onto the surface of the microparticle and an adjuvant encapsulated within the microparticle. Dependent claims recite the polymer as poly(L-lactide), poly(D,L-lactide), or poly(D,L-lactide-co-glycolide) (PLGA) and recite the antigen as HIV gp120.

Levy et al. teach microparticles comprising an anionic or nonionic detergent (page 16, first paragraph) and a polymer selected from a polyanahydride, a polylactide, a polyglycolide, and a polycaprolactone, among others (see the paragraph bridging pages 7 and 8). Levy et al. teach a preferred polymer as PLGA (page 8, lines 4-10). Levy et al. teach the particles as comprising biologically active molecules in combination adsorbed onto the surface and encapsulated within (page 7, first paragraph and page 20. lines 11-15). Levy et al. teach representative biologically active molecules as a nucleic acid (page 11, line 1; page 12, lines 3-4 and 14-15; page 14, lines 17-20; and page 15, lines 16-19) and an adjuvant (see the sentence bridging pages 8 and 9). Finally, Levy et al. teach AIDS (HIV-1) as a preferred antigen (page 10, lines 17-18).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 10, 11, 13, 14, 43-47, and 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Moore et al. (Vaccine, 13/18:1741-1749, 1995) and Haynes et al. (AIDS Research and Human Retroviruses, 10, Suppl. 2:S42-S45, 1994)

The claimed invention is drawn to composition comprising a microparticle comprising a cationic or anionic detergent, a biodegradable polymer (PLGA), a polynucleotide (plasmid DNA) encoding a biologically active antigen (HIV gp120) adsorbed onto the surface of the microparticle, an adjuvant encapsulated within the microparticle, and a pharmaceutically acceptable excipient.

Levy et al. teach microparticles comprising a cationic and anionic detergent, a polymer (PLGA), and biologically active molecules (with a nucleic acid and an adjuvant disclosed as representative

molecules) adsorbed onto the surface of the particles and encapsulated within the microparticles. Levy et al. teach formulating compositions comprising the microparticles and a pharmaceutically acceptable excipient (see page 24, line 19, through page 26, line 4). Levy et al. teach that the microparticles provide sustained release of bioactive agents *in* vivo (see the abstract). Levy et al. teach a preferred biologically active molecule as an AIDS (HIV) antigen (page 10, lines 17-18). Levy et al. does not specifically teach the HIV antigen as gp120, as in the present invention, and does not specifically teach a nucleic acid encoding HIV gp120 adsorbed onto the surface of the microparticle in combination with an adjuvant encapsulated within the microparticle.

Moore et al. teach that recombinant HIV-1 gp120 is the HIV antigen of choice for incorporation into microparticles. Moore et al. teach that microparticles incorporating gp120 provide a safe and effective vaccine delivery system for induction of cell mediated immunity to HIV-1 (see page 1741, abstract, and page 1742, *Materials and methods, gp120 microparticles*).

Haynes et al. teach that HIV-1 gp120 plasmid DNA-coated gold microparticles injected into epidermal tissues results in *de novo* production of antigen-specific humoral and cytotoxic cellular immune responses directed against HIV-1.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated plasmid DNA encoding HIV-1 gp120 antigen as the biologically active molecule of choice into the microparticles taught by Levy et al., in order to formulate a safe and effective vaccine composition which would elicit production of both humoral and cellular immune responses against HIV-1 over time.

Claims 1-7, 10-15, 43-47, and 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Cleland et al. (U.S. Patent 5,643,605).

The claimed invention is drawn to a composition comprising a microparticle comprising a cationic or anionic detergent, a biodegradable polymer (PLGA), a polynucleotide (plasmid DNA)

encoding a biologically active antigen (HIV gp120) adsorbed onto the surface of the microparticle, an adjuvant (an aluminum salt) encapsulated within the microparticle, and a pharmaceutically acceptable excipient.

Levy et al. teach as described *supra*. Levy et al. do not specifically teach the nucleic acid as adsorbed onto the surface of the microparticle with the adjuvant encapsulated within, do not specifically teach the biologically active molecule as specific for HIV-1 gp120), and do not teach the adjuvant as an aluminum salt.

Cleland teaches PGLA microparticles comprising an antigen (nucleic acid, polypeptide, or viral antigen, such HIV gp120) adsorbed onto the surface of the microparticle and an adjuvant encapsulated within (see the abstract; column 6, lines 13-31 and 24-25; and column 10, lines 5-6). Cleland teaches an exemplary adjuvant as aluminum hydroxide (column 9, lines 59-63). Cleland teaches that microparticles comprising an antigen adsorbed onto the surface and an adjuvant encapsulated within are effective single shot vaccines (see column 1, lines 34-45).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have encapsulated an adjuvant, as taught by Cleland, in the microparticles taught by Levy for an effective single shot vaccine preparation. One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to incorporate nucleic acid encoding HIV gp120, as described Cleland, as the biologically active molecule because Cleland teaches HIV gp120 is an antigen of interest for formulation into microparticles.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over either of over Levy et al. in view of Moore et al. and Haynes et al. or Levy et al. in view of Cleland et al. as applied to claims 1-7, 10, 11, 13, 14, 43-47, and 54-57 above, and further in view of Cox et al. (U.S. Patent 5,902,565).

The claimed invention is drawn to a microparticle comprising a cationic or anionic detergent, a biodegradable polymer (PLGA), a polynucleotide encoding a biologically active antigen adsorbed onto

the surface of the microparticle, and an adjuvant (aluminum phosphate) encapsulated within the microparticle.

Levy et al. in view of Moore et al. and Haynes et al. or Levy et al. in view of Cleland et al. teach microparticles comprising an anionic or cationic detergent , a biodegradable polymer, a polynucleotide encoding a biologically active antigen adsorbed onto the surface of the microparticle, and an adjuvant encapsulated within the microparticle, as was set forth *supra*. None of Levy et al., Moore et al., Haynes et al., or Cleland et al. teach the adjuvant as aluminum phosphate.

Cox et al. teach aluminum phosphate as an adjuvant that is effective when used in microparticle vaccine compositions (see the abstract and column 14, claims 1 and 2).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have incorporated aluminum phosphate as the adjuvant of choice into the microparticle formulations of either of Levy et al. in view of Moore et al. or Haynes et al. or Levy et al. in view of Cleland et al. based on the teachings of Cox et al.

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over either of over Levy et al. in view of Moore et al. and Haynes et al. or Levy et al. in view of Cleland et al. as applied to claims 1-7, 10, 11, 13, 14, 43-47, and 54-57 above, and further in view of Carlo et al. (U.S. Patent 4,413,057).

The claimed invention is drawn to a microparticle comprising an anionic or cationic detergent (specifically hexadecyltrimethylammonium bromide), a biodegradable polymer, a polynucleotide encoding a biologically active antigen adsorbed onto the surface of the microparticle, and an adjuvant encapsulated within the microparticle.

Levy et al. in view of Moore et al. and Haynes et al. or Levy et al. in view of Cleland et al. teach microparticles comprising an anionic or cationic detergent , a biodegradable polymer, a polynucleotide encoding a biologically active antigen adsorbed onto the surface of the microparticle, and an adjuvant

encapsulated within the microparticle, as was described *supra*. None of Levy et al., Moore et al., Haynes et al., or Cleland et al. teach the cationic detergent specifically as hexadecyltrimethylammonium hydroxide.

Carlo et al. teach hexadecyltrimethylammonium hydroxide as a cationic detergent for use in formulation of vaccine compositions comprising Group B streptococcus antigen (see columns 23-24, claims 1 and 2).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have used hexadecyltrimethylammonium hydroxide as the cationic detergent in the microparticle formulations of either of Levy et al. in view of Moore et al. or Haynes et al. or Levy et al. in view of Cleland et al. based on the teachings of Cox et al. of its suitability for vaccine compositions.

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over either of over Levy et al. in view of Moore et al. and Haynes et al. or Levy et al. in view of Cleland et al. as applied to claims 1-7, 10, 11, 13, 14, 43-47, and 54-57 above, and further in view of Macfarlane (U.S. Patent 5,010,183).

The claimed invention is drawn to a microparticle comprising a cationic or anionic detergent (sodium dodecyl sulfate), a biodegradable polymer, a polynucleotide encoding a biologically active antigen adsorbed onto the surface of the microparticle, and an adjuvant encapsulated within the microparticle.

Either of Levy et al. in view of Moore et al. and Haynes et al. or Levy et al. in view of Cleland et al. teach microparticles comprising an anionic or cationic detergent , a biodegradable polymer, a polynucleotide encoding a biologically active antigen adsorbed onto the surface of the microparticle, and an adjuvant encapsulated within the microparticle, as was set forth *supra*. None of Levy et al., Moore et al., Haynes et al., or Cleland et al. teach the anionic detergent as sodium dodecyl sulfate.

Macfarlane teaches sodium dodecyl sulfate as an anionic detergent routinely used in DNA preparations (see column 1, lines 35-46).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have used sodium dodecyl sulfate as the anionic detergent in the DNA-microparticle compositions of either of Levy et al. in view of Moore et al. and Haynes et al. or Levy et al. in view of Cleland et al. according to the teachings of Macfarlane.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Mathiowitz et al. (WO 95/24929) teach that efficient introduction of exogenous DNA and long term expression of the DNA *in vivo* is achieved by incorporating the DNA into a microparticle (see the abstract).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Official FAX telephone number is (703) 872-9306 and the After Final FAX telephone number is (703) 872-9307. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
Patent Examiner